HEPATITIS C

Hepatitis C is an emerging disease in the United States and worldwide. Before 1990, transfused patients were vulnerable to an unidentifiable liver disease agent(s) known only as non-A, non-B hepatitis. Cloned and sequenced more than a decade ago, hepatitis C virus (HCV) was identified as the cause of most of these chronic infections. Chronic hepatitis C infection can lead to liver inflammation, cirrhosis, and cancer. HCV remains the leading cause of liver transplants in this country. Rapid improvements in HCV diagnostics have occurred both in terms of antibody detection and the presence of the virus directly, making the supply of blood and blood products in the United States very safe. New infections continue at the rate of 25,000 cases a year in the United States *(www.cdc.gov/ncidod/diseases/hepatitis/c/fact.htm).*

Today, injection drug users are at highest risk, yet transmission also occurs sexually (greatest with multiple partners) as well as through other mechanisms involving inadvertent exposure to contaminated blood. Estimates today indicate that HCV is carried by more than 170 million people worldwide, with 4 million in the United States alone *(www.cdc.gov/ncidod/diseases/hepatitis/c/fact.htm).* Approximately 75 percent of those infected become chronic carriers, many of them unknowingly. They manifest no overt signs of liver morbidity for decades while their livers are undergoing active disease progression *(www.cdc.gov/ncidod/diseases/hepatitis/c/faq.htm#1g).*

NIAID has aggressively pursued the expansion of HCV research through its development of the Hepatitis C Framework for Progress. With the aid of participating Institutes and Centers, an NIH-wide framework was drafted that incorporates the different missions into a cohesive global plan. The final plan was reviewed by outside experts and has been approved by both NIH Institute and Center Directors and the NIH Director. The following research goals were identified in the framework:

- Understanding transmission modes to develop effective intervention strategies;
- Understanding pathogenic mechanisms and disease progression to develop treatments;
- Characterizing host immune responses to infection to develop vaccines and prophylactic measures as well as therapeutic measures;
- Defining viral replication and recovery with therapy as well as developing new therapeutic strategies;
- Investigating clinical manifestations to develop noninvasive methods to evaluate current disease state, to predict outcomes, and to prevent or reverse disease progression; and
- Defining effective prevention and intervention strategies to improve health.

The tools needed to develop these goals include tissue culture systems, small-animal models, well-defined clinical cohorts, and research and reference reagents and tools.

Current therapies include various forms of interferon, an interferon-ribavirin combination, and long-lasting forms of interferon with and without ribavirin. Each iteration of therapy has resulted in improved response rates. Unfortunately, these drugs have a significantly lower success rate in African Americans and in patients infected

with the viral genotype that predominates in the United States. Genotype refers to the genetic makeup of an organism or a virus. At least six distinct HCV genotypes have been identified, and genotype 1 is the most common genotype found in the United States. Studies suggest that African Americans with genotype 1 treated with interferon for HCV have a lower end-of-treatment response than whites. NIAID funds both basic research and product development on viral therapeutic targets, including inhibitors of viral components such as the polymerase, protease, helicase, and internal ribosome entry site as well as other viral components critical for replication.

Extramural investigators developed HCV cell lines that are now validated as *in vitro* antiviral screening tools. NIAID supports two of these systems via its *in vitro* screening contract programs; they are used by both academic and corporate scientists *(www.niaid.nih.gov/dmid/viral).*

HCV is able to subvert the immune response, a process called immune evasion. Thus, defining and overriding these evasion strategies through rational design of vaccines and immunotherapies is an area of ongoing research and application to development by NIAID extramural-supported scientists around the country.

NIAID intramural and extramural investigators also are conducting and supporting a number of research activities that will help pave the way for the development of HCV vaccines. Recent efforts toward the development of vaccines have been and remain primarily related to the identification of immune responses, both in infected humans and in experimentally infected chimpanzees, and their correlation with protection. This year NIAID launched a phase I trial using Chiron Corporation's prototype E1E2 vaccine. This study is intended to evaluate the safety, tolerability, and immunogenicity of a vaccine in healthy, uninfected human subjects.

The extramural program of NIAID has initiated two activities to further broaden research and development activities and enhance progress. The first activity is acquisition and provision of HCV research reagents. These reagents are obtainable via the AIDS Research and Reference Reagent Program *(www.aidsreagent.org).* Other reagents are available through the NIH Tetramer Facility (*www.niaid.nih.gov/reposit/tetramer/index.html)* and the NIAID Reference Reagent Repository (*www.bratonbiotech.com/braton11.htm).* The second activity is the development of an annotated HCV sequence database by Los Alamos National Laboratories *(http://hcv.lanl. gov/content/hcv-db/index).*

In 2002, NIAID cosponsored the Management of Hepatitis C, 2002, Consensus Development Conference. The meeting was convened to provide an update to a 1997 conference on the same topic. Among its recommendations for future research, the panel gave top priority to the development of reliable and reproducible HCV cultures, which will advance the understanding of HCV biology and mechanisms of drug resistance and aid vaccine development. The panel also urged the establishment of a hepatitis research network that would conduct research into the natural history, prevention, and treatment of hepatitis C. NIAID supports a robust hepatitis C research portfolio that encompasses many of these areas. In particular, NIAID supports the Hepatitis C Cooperative Research Centers Network, which unites basic and clinical

researchers investigating hepatitis C infection and the disease process to identify new and better means of prevention and treatment. Through this network, NIAID supports clinical research that emphasizes studies in special populations heavily affected by HCV such as African Americans who respond poorly to standard therapies. NIAID also continues to provide partial support for the ancillary studies of the HALT-C trial of the National Institute of Diabetes and Digestive and Kidney Diseases. The trial is evaluating the impact of long-term therapy on disease progression, including virologic and immunologic responses and their association with recovery.

Scientists at NIAID's Division of Intramural Research (DIR) are conducting research on the mechanism that leads to the transition from asymptomatic infection to chronic infection and recovery in response to therapy. This work includes studies of the relative importance of the virus versus the host immune response in determining the outcome of infection. Scientists are using standardized amounts of a single genetic strain of HCV to study the natural history of chronic hepatitis C in chimpanzees by mapping the mutations that occur over time. Additional studies will focus on the types of genetic mutations that help HCV evade the immune system and on the types of antibodies produced during the early immune response. In addition, various approaches to answering key questions about HCV pathogenesis and the host immune response are being pursued by extramural scientists. Understanding these phenomena will allow the development of new tools for hepatitis C treatment and prevention.

In addition, NIAID intramural investigators are accelerating research to develop an HCV vaccine. To this end, they have prepared and standardized doses of HCV that can be used to test the effectiveness of candidate vaccines in the chimpanzee and have distributed this key reagent to the scientific community. Intramural scientists have developed and tested candidate DNA vaccines for HCV in chimpanzees. The scientists also are evaluating vectored vaccines. Although these experimental vaccines did not prevent infection, they did modify the course of the infection.

Vaccine studies are hampered by the lack of a small-animal model or an *in vitro* system in which to study HCV and fine-tune possible vaccine formulations. To address both the lack of a small-animal model and the poor growth of wild-type HCV *in vitro* (cell culture), DIR researchers are genetically manipulating HCV to identify an infectious cDNA of HCV that can replicate *in vitro* and *in vivo*. Preliminary results of this work showed that mutations allowing replication of the HCV genome in cell culture markedly weakened the virus for replication *in vivo*. This finding suggests that extrapolation of results obtained in the *in vitro* system to the clinical setting must be done with caution.